DR. CONTI: I think I have just told you that we can't do all of these tests, so you need to tell us which ones you are worried about, so we can figure out whether we can actually do the tests or not because, frankly, I am not in the position to develop a test for metal hydrides or something like this at an academic institution necessarily, it is just not possible to do some of these things.

MS. AXELRAD: You could contract it out, for example. We are not just dealing--I mean if we wanted to limit this regulation to the drugs we know, FDG, ammonia, water, maybe we could do that, but we are not doing this. We are writing GMPs for all PET drugs, both those we know now and those that may come in the future, and so it puts us in a very difficult position because we don't know whether you might start manufacturing a PET drug which has an ingredient or a compound in it that might not be picked up by just--you know, the process just doesn't work, and that could cause a real problem.

DR. CONTI: That is not what we are talking about here, Jane. We are talking about issues related to the materials used in the preparations of a drug and making sure that they are what they, in fact, are.

You are putting an extra burden on the academic centers to come up with some way of doing a quality control check on manufacturers that are producing these materials on

the outside, and I am telling you that that is not going to work, so, you need to work with that.

DR. KASLIWAL: I think one way maybe ICP can help out there is in qualifying the vendor for everybody, so individual person doesn't have to do that, establish the reliability on a central basis. I mean what is reliable? Just looking at somebody's face, is that reliable? Sometimes it is.

MS. ROBERTS: We understand what you have said so far about the testing and the COAs. We will have to take that back for internal discussion, however, we think it is important for you to test, to do one specific test off the COA for the major components that are going into the drug products.

MR. SWANSON: One area of relief there, a specific comment that you definitely need to look at is if we are using any component that is already FDA approved, is either a drug or a device, okay, it seems like you ought, I mean as part of your FDA--normal saline, 0.9 percent sodium chloride for injection, sterile vials, okay, that are commercially available. I mean you are requiring all these people to go through all the same process controls to ensure that what they are releasing meet acceptance criteria. Now you want us to go back and retest these things?

So, I think that is one area where you could

probably provide some relief.

DR. KASLIWAL: Dennis, if you look at the model applications, I think there is a relief for presealed, if you buy pre-sterilized, sealed vials, as well as saline, if it is indeed an approved product, and by that means, 0.9 percent sodium chloride, let's say, from a manufacturer that has an NDA for that or an ANDA for that, if you want to prepare the 0.9 percent sodium chloride in-house, that is not an approved product.

MR. SWANSON: I don't have a problem with what you just said, but I understand your model ANDA submissions are not the regulations, so perhaps your regulations could help address that issue.

MS. ROBERTS: That point is well taken. We will look at that.

MR. KUHS: On the final section, Section (e), the last sentence that we need to keep records of the disposition of rejected material and the expiration date, we ran into a situation in Peoria where we had some glass vials that had a Certificate of Analysis that were shorted in another facility, and they sent 25 vials to another facility to use, and the issue comes with reconciliation of the inventory, of control of all of the components, containers, closures, material, and the inventory that was at the end did not reconcile with what was received, and so there was a

question on why didn't we have a reconciliation of inventory.

I think that we have resolved this. There was a 483 issued on that. I would have to ask Ken for sure, but I think we resolved it in that we weren't required to keep an inventory or reconciliation of inventory at the end of disposition, in other words, if we had a bad vial of Kryptofix, people just toss it, they don't mark it and say there isn't a reconciliation of inventory, and I think that that could be a problem.

MS. ROBERTS: What this specifically is talking about here is if you test a component and it doesn't meet, it is rejected, it fails, then it should be marked as rejected, you should write in under wherever you tested it that it wasn't any good, that this failed and it was disposed of.

MR. KUHS: Let me give you an example of that. Oftentimes you will get a shipment of a case of vials that are used for collection, a final container, and it was dropped during shipment and two or three vials are broken. You throw you the vials you didn't use, but we don't make a note anywhere that two vials were broken.

It is an issue that while it seems insignificant now, when we talk about reconciling inventory at the end, it does become a problem, and I don't think anyone keeps track

of vials that for some reason when you pull the pop top off, you didn't do it right or the container crimped or something else, you just toss it, you don't make a record in your inventory anywhere that something was wrong with it or that you destroyed it.

MS. ROBERTS: That wasn't the intended purpose of this specific part, and that is something that I can definitely address in the guidance, which I agree with you that if you throw out a vial if it's broken, you are not going to be able to use it anyway, so that is something that I will take under advisement and make sure that it's delineated in the guidance document.

MR. KUHS: Okay. I think it's just the final reconciliation doesn't really lend itself well to small amounts of inventory that are generally kept on hand at a PET center.

DR. CONTI: If I could go back for one more minute to (2) again, on this issue of testing. One issue comes to mind where you have a commercial entity that may buy these components in bulk, and then is able to, because they have purchased a certain amount or they have a certain level of operation, have the infrastructure in place to do such identity testing, and that may amount of the same bulk shipment that is used for 20 cyclotron operations.

In that configuration, perhaps that is one way of

looking at the difference between a commercial entity and an academic institution, which would have to actually duplicate at each site that same testing or contract with somebody to do that type of testing. So, I think that needs to be taken into consideration, as well.

MS. ROBERTS: Any other comments on this particular section?

Then, we will move on to Subpart F, Production and Process Controls, and as quickly as we can get through this, then, we can go to lunch.

MR. SWANSON: Item (c), you talk about information that needs to appear on the master production and control record. In Sub-item (1), you have the name and strength of the PET drug. The strength is going to be batch-specific, so we can't define a strength in a master production record per se.

MS. KEPPLER: For those of us that are a little less familiar with this, could you explain the difference between the written production and process control, the master production and process control, and the batch production and process control? It wasn't clear to me.

MS. ROBERTS: The master production and process control generally is your master record of how, based on your knowledge of the product, you are going to produce that product. It includes all of the steps that you are going to

follow, everything that is going to be done, spaces on the formulation page for how much product, how much component you will be putting in, spots for weighing out the component, and a detailed production listing of the steps that you are going to follow with signoffs, initials, parts for, you know, that we have completed that step.

Usually, what it also consists of is whether it is the most recent production record. You have a master. You keep the one master, and how we usually see it done is off the master you make your copies for your batch production records, and that batch production record, you actually fill in when you are producing your batch from a master.

A master lays out the guideline that you will follow for making that particular batch or that particular size of the batch.

That is a master that is kept, and each time you may change your formulation or you change a different processing step, you need to make a new master production record, keeping in history the old ones also, and they are usually dated as to which is the most recent one to follow.

MS. KEPPLER: So, the master is a compilation of all your batch production records with the most recent one on top as being the one done?

MS. AXELRAD: No, I think the master is like the recipe, and then the batch record is a notation that you

followed the recipe and what you did for the specific batch.

MS. KEPPLER: Are they on the same sheet of paper or you would have your recipe--but she was talking about filling in the blanks and places to initial on the master.

MS. AXELRAD: Right.

MS. KEPPLER: That you would then xerox and use for your batch.

MS. ROBERTS: That is exactly what it is. The master production record is a template of everything, of the whole recipe that you are going to follow with all the blanks. You keep that as your master, and every time you go to produce a batch, you make the copy, you give it out, and that is the one that they will fill in the blanks for when they produce the batch.

MR. SWANSON: You might also state that when you make that copy, you are required to certify that that copy of your batch record is an accurate reproduction of the current master formula card, so somebody has to sign off on that, okay. Another step.

DR. KASLIWAL: Just a comment on that inclusion of the strength on the master production record. You can probably include the range of the strength that you would put in your model application that you have validated, and your batch's specific strength would be on the batch record.

MR. SWANSON: All I am saying is it can't be a

specific value.

MR. FERRIS: With respect to the issue of strength, the name and the strength of the drug, as you define strength here, you are talking about concentration. If you carry that over to this particular section, that would basically indicate to me anyway, in my read of this, that you wouldn't have a batch size, you would have a concentration that you would specify.

In other words, I could make 25 millicuries to 24 curies. As long as I diluted that in my final finished dosage form to the appropriate concentration, what you call strength, then, that would be okay, but that doesn't make sense.

DR. KASLIWAL: You would define a batch size in the model application.

MR. FERRIS: That should be millicuries. That is millicuries.

DR. KASLIWAL: Right, but the strength for purpose is the concentration, but the batch size will be the total, yes, millicuries.

DR. CONTI: I have another comment on the (5), the theoretical yield again, as we talked about earlier, that needs to be modified, so just to note that.

Down on Section (7)(h), the two tests, are these duplicate or different tests, and where do we get that

information from?

MS. ROBERTS: This is just explaining the reserve sample portion. It is a reserve sample that you would keep in case you need to retest for any particular reason, and we say that you should keep enough for two tests in case the one is a failure or a problem, you will have enough there to do a retest to confirm whatever result you got. That is what is meant by that.

MR. KUHS: I have two comments on that. Number one, it is very often that the entire batch may be administered to a single patient, and that came from a different definition a long time ago.

The second one is if we are making entire vials to be redistributed by a radiopharmacy, oftentimes the entire manufactured batch goes to that radiopharmacy. Are you saying that we need to take a sample out of that batch and put it into a separate vial for a reserve sample?

This is an issue that did come up again in Peoria, that they were making a separate entire vial, manufactured vial, which was delivered to a radiopharmacy for redistribution without keeping a reserve sample out of that, and if you keep a reserve sample out of it, and transfer it to an additional vial, doesn't that destroy the integrity of the original sample?

DR. KASLIWAL: I think that probably we will need

to discuss whether a sample ought to be withdrawn or the vial ought to come back to the manufacturer. We don't know what is going to be the proper way.

MR. KUHS: There are a number or regulations that actually prevent return of vials to the manufacturer, so that is probably not an appropriate solution, but it was an issue.

DR. CONTI: The other thing about that question is whether or not you do these pre-tests, pre-batches for certain isotopes also for the O 15 in particular. You are not going to be taking a sample necessarily out of the one you are actually delivering, but you have done your analysis on the prior one.

If it is a gas or something like that, how do you save that sample for a retest later?

MS. ROBERTS: I actually had the same question that you all are bringing up, and I wanted your input on this issue, on how feasible it is, how you would do it, if it is absolutely necessary.

I would think that it might be in certain instances, for certain products, where there is different ligands or there is other problems where a product may--there could be something in the product that you don't find about until later and you want to retest the product to find out what it exactly was, so you can fix it later.

Is there any instances where that would happen, and it would be beneficial? I thought it was in the Peoria instance.

MR. KUHS: I think you can probably address that by doing a periodic reserve sample, and not necessarily one out of every batch, and that may be something that is defined in the way the application is submitted, that you agree on a monthly, bimonthly, six-month basis to keep a reserve sample for periodic testing.

I am not sure how to resolve that, but that is just a suggestion.

MR. FERRIS: It is intriguing to me, with 110-minute, half-life material, doing an investigation 30 days later, and typically, the tests exclude sterility and pyrogenicity, that is not what you usually mean for the testing, so if we exclude those two, what tests might be useful, that would give us insight as to what happened?

MS. ROBERTS: Is there any instance where it would be important that where an organic solvent would have gotten into the product, that you would want to retest to find out if that indeed was the instance or the problem?

That is the specific thing that I was thinking of in this case.

MR. FERRIS: It may have dissipated 30 days later.

DR. KASLIWAL: I think the chemical testing

obviously, because radioisotope is gone. You could repeat chemical testing, and if the safety problems arise, more than likely they probably arise due to chemical.

DR. BARRIO: We seem to be focusing clearly on radiopharmaceuticals that are being used in the clinic, but, of course, this is intended to be used in research, too. If a PET center produces 10 or 15 compounds a day either being used for the clinic or be used for research or be used for animals or be used for studies, all of these have to apply.

Therefore, you know, I think it is difficult to envision how you could do many of those things even for research preparation, that have less control, of course, because they are research preparations. Sometimes we are beginning to produce a product, and they are more difficult to get this kind of control we should have daily for human injections.

MS. ROBERTS: We will have to revisit this, and I will take a lot of your comments. There might be a way where we can deal with it on an application by application basis, but my fear with that is for products that don't have an application or may not in the interim, so it is something that we will need to talk about.

I would appreciate also--I guess you are all staring at me like why do you think we need to keep this--and the particular instance was from the research that

I have done with Peoria and I thought that there might be other organic solvents or other problems even if you get a pyrogenic reaction in a patient, you might want to go back and retest your sample also.

I can think of a couple of reasons why. If you could tell me why it is not feasible to do that?

DR. CALLAHAN: For one thing, organic solvent contamination is a release criteria, so you have done that before you released it. They are not going to grow into it, if anything, they are going to go away over time, so that example in the application, residual organic solvents is a release criteria, so you know that before you even release it.

MR. SWANSON: Okay. So, I have a reserve, I mean what is the purpose of the reserve sample testing, am I going to recall this lot? I can't. It has already been used. It is a batch size of one, it has already been injected in everybody, so it seems to me like if I have suspicioned a problem with organic solvents in my product, I am going to run my next batch, and I am going to take--I am taking a look at it as an end release criteria anyway, okay, I am going to go back and look at my process.

I am not sure what the purpose--yes, reserve samples have a purpose, I think, in traditional drug manufacturing, but I am not sure if that purpose applies

here, I am not sure what I can do about it.

MS. ROBERTS: Does any PET center at this time keep any reserve samples for any purpose?

MR. SWANSON: We keep vials to go back for sterility testing, but I am not sure that is an appropriate use of reserve samples.

MS. ROBERTS: Why does anybody else keep them? Is it only for sterility? Is it in case there is a problem for corrective and preventive action? I would like to hear why anybody else is keeping reserve samples.

MR. WATKINS: We keep them because we thought it was a requirement to do so, but for sterility testing, number one, your sample would have to be kept under sterile conditions if it was going to be of any use to test afterwards.

You require us to test as quickly as possible after we have made the dose. There are things in th literature which would suggest that the various bugs will disappear over time, so it may not have any significance at all doing your tests later on.

I think most of us keep them purely because we thought it was a requirement to do so.

MS. ROBERTS: Okay. I thought I might have gotten like a revelation, but I guess I am not, so we will take that under consideration.

DR. CALLAHAN: Do you require that other manufacturers retain samples beyond expiration, they have to keep them way beyond expiration or not, after the product has expired, they have to retain them?

MS. ROBERTS: Yes, they are kept beyond expiry.

DR. CALLAHAN: (7)(e), production and dispensing, I would recommend maybe changing that to production and packaging area or something like that rather than the word dispensing again.

MS. ROBERTS: In here, the particular word dispensing was used for those instances where it is directly dispensed from the manufacturing area into the patient, whether it is a gas or a liquid. That is what was meant by that.

DR. CALLAHAN: Your dispensing area is going to be inside a very, very small tube that is going to go into the patient's nose or something like that. I mean this is really impractical. Dispensing in my mind means when you are preparing unit dose syringes and under pharmacy or medicine. I think we need to reserve that term for that specific activity, and not confuse the issue. That is why I suggested packaging.

In your example, that is really patient administration, not dispensing, right, because you are administering it, it is at the interface between the drug

delivery system and the patient if they are breathing a gas or a continuous--

MS. ROBERTS: That is what we had meant by that, so maybe dispensing area is the wrong word to use.

DR. BARRIO: I would like to go to (7)(f) and (g), I guess, both of them. For chemists in the field, we do validation all the time because we want to understand how our process works, of course, but what done means to us is--if I could use a very simple example--use the FDG synthesis that I am sure everybody uses.

We have a system that we understand, has components that accomplish several steps in the process, synthesis, hydrolysis, purification, utilization, but what we would like to consider validation, I guess, that is easy to understand, is we have a system. We know what we put in, and we validate that system that produces always a certain amount of a pharmaceutical that is always sterile and pyrogen-free. That could be considered an appropriate validation procedure. This is something that every one of us will deal with every compound.

I think the issue of interpretation of what validation means for the agency is a thing that I try to address, because validation could have a different meaning if we have to address issues of minimum or large amount of activities, I mean low and large, to produce a certain

amount here and there.

The other one could be validate every single step in the process or validate every instrument we use or whatever. It may be computers, as you indicate here. What I think is not only very impractical, I think it is from my personal perspective, I guess it is completely unnecessary.

I think it would very important if you could define what validation means for you and then for every one of us to really understand how to approach that topic.

MS. ROBERTS: During the last public meeting, we had talked about validation and the definition of validation, and what I said that I might expect from the standpoint of a process validation and from sterile product validation, from your environmental monitoring per se.

I had asked for examples of things that you have done as far as validation, so I could look through them and tell you, give you a read of whether it is more than I expected, what I expected, less than I expected, and I had never received anything like that.

So, now, and at this time, it is difficult for me to sit here and tell you this what I would think how you should validate your process, because each process in each center is extremely different, and your validation is based on what you are doing and what you want to prove, your process.

It could be important to validate each particular little step if it's a critical processing step. If it is not a critical processing step for your operation, you may not need to include it in a validation.

When we talk about validation, it is the definition that is written in here, yes, it's pretty vague, however, what we want to make sure that you are doing is consistently producing a product to what your specifications are.

DR. BARRIO: In the preparation of pharmaceuticals that include a synthesis process, other elements in the synthesis, not only their reaction, but sometimes modification of intermediates, all the steps. Then, based on your definition, then, we have to monitor every single step, and I feel that that is probably unnecessary because if we achieve the result that is expected, and, of course, one has to expect that the chemists or pharmacists doing that will really understand how the system works.

I mean this is a black box, but we know it is not a black box, it is a series of chemical components there, but there is a difference between going through every single component in regards to regulation versus if you go to any PET center you want, you are right, every PET center does it in a different way, but if you get from whatever system everybody is using, you go there and say, okay, you give me

10 studies in which you obtain always the same part, then, why do we need to go to every single step in the process?

I think that is crucial because this will add not only a tremendous amount of work, but I feel it is probably certainly unnecessary in many circumstances, and I agree with you, maybe in some circumstance.

I could see, for example, that when you are investigating a particular new synthesis, this is something we do all the time. I would like to do how every component works. I would like to understand whether that column does the separation I want or not. I mean this is something we do all the time, but that becomes a routine procedure, something we have done a zillion times. To require this kind of documentation is going to be so burdensome that this is difficult to believe that anybody would like to do that.

MS. ROBERTS: I understand what you are saying. You have brought up a very important point about new entities that you are manufacturing, new synthesis that you are going to validate. You are validating while or before you are starting your production.

For products that you have already been producing for so long, it wasn't my intention to require prospective validation, what we normally call prospective validation where you would go and start validating every single little piece.

I would expect that for new drug products that you will begin to bring up on line when these regulations are in effect.

What I have envisioned for products that you are already making and have a lot of history on, what you were talking about would be like a retrospective validation where you wouldn't go back to each particular little step because you have all these years or experience making the product, and you basically know what your results will be.

A retrospective and a prospective are different in those respects, and I would think that it would be fine for you for products that you have already been making for this long, to gather a lot of the data that already exists.

What I envision is that you would only have to write a protocol about what you are going to do to show that this process is indeed validated, is reproducible, which may mean that you don't need to do any additional tests. You may just need to write your protocol about what you expect it to meet, how you are going to do this, and then gather all the data to show me that indeed this process is validated.

We have done that with other older products in the drug arena, as well as a lot of firms also--it hasn't been a problem in the past, and I really don't envision you having to do prospective validation for every product that you are

currently manufacturing.

MR. FERRIS: If you are going to accept retrospective validation, then, typically, that will not include extreme limit testing.

MS. ROBERTS: I am sorry?

MR. FERRIS: If you are going to accept retrospective validation, it is not going to include extreme limit testing with respect to components, and which is typical in regular prospective validation.

MS. ROBERTS: Right, and I understand that.

MR. FERRIS: And that is acceptable.

MS. ROBERTS: We are going to have to take that under advisement, and it may be acceptable, and I envision doing a retrospective for all the products that you already have up and running, and have all of these on, unless you do encounter a problem with your process or along the lines, and you think that is part of the process, and you would need to do the extreme testing.

But if you are not encountering any problems, I wouldn't expect that you would have to go back and do that as part of retrospective.

DR. BARRIO: Then, in this context, if you read (7)(f), how do you interpret that section?

MS. ROBERTS: In that section, we are talking about in-process controls, if your PET center thinks that

you need the in-process control. For some processes you may need them, and for other processes you may not need them.

This is one is basically, whether for the critical components that you think may be a problem, that you definitely have to watch to make sure that you are going to get the product that you expect to get out at the end. That is what I would think. That is the intent of this.

DR. KASLIWAL: I think it is related to testing of in-process materials, if they are isolated. In the radiochemical operation, you probably don't have any isolatable in-process materials, but I understand the regulations are--to be used and the facilities and controls to be used.

That whole aspect starts from a starting material, was defined as a starting material, so your individual process may have or may not have in-process materials. In-process materials, we usually can designate them as components. They are in-process materials, anything beyond a starting material if it is isolatable and kept, it is in-process material and needs to be tested, according to what you designate them as is called the parameters.

DR. CALLAHAN: Could you give us an example in, say, FDG terms, is there anything that relates to that based on your definition of in-process materials that are isolatable?

DR. KASLIWAL: If it was defined as a starting material, anything beyond the starting material is an in-process material. For example, the mannose triflate is an in-process material, it is not a starting material according to the definition, if you go back and look at the definition in Drug Substances guidelines, and we will take it as a key intermediate. It's an in-process material, and you can accept it on the basis of COA.

DR. BARRIO: You are saying that mannose triflate is not a component of the final preparation. It is a material that is used to produce a radiopharmaceutical.

DR. KASLIWAL: Right.

DR. BARRIO: And therefore, should be controlled with a Certificate of Analysis or whatever.

DR. KASLIWAL: You could do that, right, and in the application are the criteria for it. If you read the definition, component means any ingredient intended for use in the production of a PET drug, including any ingredients that may not appear in the final PET drug product as well as any packaging materials and container-closure system.

DR. BARRIO: Well, this is similar to the discussion we had a few minutes ago. I mean we are talking about the same thing, right?

DR. KASLIWAL: How you define that.

DR. BARRIO: I mean how to really define the

quality of the product.

DR. KASLIWAL: For mannose triflate, if you look at model application, I think you have to define how you accept it, and, you know.

DR. CONTI: To be honest with you, I would rather be considering testing the mannose triflate than sodium chloride.

DR. KASLIWAL: And I agree with that.

DR. CONTI: I think there is a level of comfort.

DR. KASLIWAL: I agree with that except that if the sodium chloride is used in the formulation.

DR. CONTI: I am talking about the components, the manufacturing process. I mean there are certain things that just seemed a little bit onerous.

MR. FERRIS: In the discussion about validation, are you including computer system validation, as well, with respect to retrospective?

MS. ROBERTS: Yes. If you have already been using that same program to produce that same drug product for all those years, that system would need retrospective validation also.

DR. CONTI: What if you upgrade your software?

MS. ROBERTS: If you have already prospectively validated the whole system, and you upgrade to a different version, that would still be a validation or more of a

verification that this upgrade is still working, you are still achieving the same thing.

DR. CONTI: Wait a minute now, because now if I have a 10-year track record of making FDG with a certain piece of software, you are telling me I now have to do a prospective validation when I upgrade my software? That changes the whole configuration.

MS. ROBERTS: If you have already retrospectively validated that program, and it's working fine for what you needed, when you upgrade to a new version, you have to do a smaller validation, it is still a validation, to make sure that everything is still working the way it should be working for that change in software.

DR. KASLIWAL: I think if you read the USP, even USP says you do have to verify that upgrade if there is a change in computer software program. If you want, I can read the USP language.

DR. CONTI: But the validation could be just again the reproducibility of the--

DR. KASLIWAL: Verification of the batches.

DR. CONTI: Right.

DR. KASLIWAL: I think that is what Tracy was saying.

DR. BARRIO: Then, you upgrade your system, and if it produces FDG according to the specification, you are

done. You don't need to go and really reanalyze.

MS. ROBERTS: In essence, yes, if everything is continuing to work and you expect--but you need the paperwork behind it that says I put in a new version of software, I am going to make sure that my next three batches still work the same way, all my testing is still right, there is no glitches.

You produce your three batches. Your validation is done. It is signed off, everything looks okay. There is no problems with the new upgrade.

MR. SWANSON: Along the same lines, the USP statement that you quote was actually criticized in several comments that came back in that there probably needs to be some cutoffs for types of changes that require revalidation versus types of changes in the computer software that wouldn't require revalidation.

You may change the software for insignificant reasons, so there needs to be some clarifying information in your guidance document again I think along that line, because I think that is a valid criticism.

MR. KUHS: I have a question on (c)(2). We don't have a good definition in our definitions in front of what constitutes a dosage unit. That is a little vague to me. I am not quite sure what that means.

We are dealing here with something that changes

over time, we are dealing with amount of radioactivity for a certain weight or volume, but that changes over time, and I am not quite sure how this addresses this.

We can give you the total weight or the total volume of what the dosage unit is depending on what that is, but is the dosage unit an entire vial, is the dosage unit a single injection, is the dosage unit a millicurie or a mL? That whole section doesn't mean much to me.

MR. SWANSON: I really think it needs to be changed to specify per batch or lot, and not dosage unit.

DR. KASLIWAL: I think this is intended to be--and we will look at that--it is intended to be the batch formula that you use.

MR. SWANSON: Along the same lines, what is the difference between (2) and (4)? You don't differentiate between an active ingredient and a component in your definitions, so I am assuming a component is an active ingredient, and so I don't see any difference between the two.

MS. ROBERTS: I think there is a differentiation in there for that, and if there is not, we will make one.

MS. AXELRAD: We do say any ingredient, but traditionally, in our regulations, there is different kinds of ingredients. There is active ingredients and other components is usually I think the way it is done.

So, we had indicated that we needed to add a definition of inactive ingredient, which would differentiate it from a compound.

I don't know about the rest of you, but I am badly in need of breaking.

Are there any very quick, maybe one or two questions from the people in the audience?

MR. CHALY: I am Thomas Chaly from North Shore University Hospital.

I don't think it is fair to ask us to do the chemical testing of all the reagents that we are using for PET production. For example, we are using anhydrous ether, acetonitrile, Kryptofix, and the precursor for that.

If we have to do all the testing for all these, we need a lot more staff, I don't think that a small hospital like us can afford that, and I don't think it is necessary. We have been doing this for the last 15, 20 years, using the same kind of ether, same kind of acetonitrile, and it doesn't make any sense to me.

They are manufactured by good manufacturers, Aldrich, Sigma, and all these companies.

Another thing is the validation for each indices, we do that in the beginning of a new synthesis. When we develop a synthesis, particular synthesis, we do like a four of five synthesis in the same fashion. We take the sample

out. We do a sterility and a quality control testing.

For example, in the case of when we develop F-dopa, we had to analyze the mercury situation there. We did four or five synthesis like that. We send out the sample outside the company, and did the checking for the mercury, the amount of mercury that can be found in the sample. This, we validate all the time. We have done that.

If we change from one to the other, suppose we buy a new synthesizer, we validate that machine before we start using that for patients. We do three or four synthesis. We do the sterility testing on that one. So, that all is validated.

MS. ROBERTS: Then, I guess you would meet the requirements under retrospective validation. That is exactly what we mean is that if you have done all this validation testing, you just need to put it together and be able to put your hands on it when somebody comes in and asks for it.

MR. WATKINS: I am a little bit confused at the moment as to what is a starting material and what is an in-process component. I guess the only starting material for fluoride, for example, is O-18 water, but I think chemists would normally think of triflate as being a starting material, and not an in-process component.

MS. AXELRAD: I think we need to discuss that

among ourselves. I have some questions, too.

MR. WATKINS: The other thing was on identification. The indication was we could some tests ourselves to identify a material, but each one of those instruments, if I take it to the chemistry department, I run an NMR or something, which would be a good way to determine the purity of triflate, that instrument would have to be validated, as well, so it is not quite as simple as it is made to appear here.

MS. ROBERTS: I just have a question, that if that instrument is being used for any other testing within a facility, I would think any academic facility or anybody that is using it for research would have that machine qualified and calibrated to meet most of the standards to make sure it is working properly, and if that is the case, indeed, then you should have no problem then in meeting the requirements under the laboratory control for the calibration and making sure that the equipment is okay for its intended use.

DR. CONTI: But by the very same argument, though, I could say exactly the same thing for the people that we bought the supplies from. It is a circuitous argument you are making here, because I could say that Aldrich also does quality control on their instrumentation when they produce these materials and test them.

So, if we get a Certificate of Analysis, it is sufficient given the fact that we also test the final product, in my opinion, and I think the opinion of both the public here, as well as this table.

DR. KASLIWAL: I guess the issue is most drug product manufacturers, they do identity tests, as a precaution, I would say, so that their final batch, because there is a lot money invested, doesn't go bad.

So, you build that quality in. So, this is the risk you are taking whether, you know, and you need to evaluate that in light of your batch sizes.

The other issue is the reason why we require that to do is I think in my mind at least, is that sometimes if people don't do it, and if there is a lot of money at stake, people--if the batch is borderline or failing, and that is the reason we require them to do that.

DR. CONTI: If the batch has failed, the system, because you test every product, it is rejected by your own criteria that you have established. Again, I mean this is the difference between testing every batch and testing only samples of batches produced in the pharmaceutical business.

MS. AXELRAD: I think we should break for lunch.

You will have a chance. Is it on this particular section?

DR. HUNG: Yes. I just want to ask a question

about when you submit an ANDA or NDA, do you have to submit a very specific GMP plan for your facility, and if so, can the inspector use that plan that you submit to the FDA to inspect the facility?

MS. AXELRAD: No, and especially in this case, since we won't have written the GMPs yet, you won't be expected to submit anything with regard to compliance with GMPs because we will have to figure out what they are going to be.

Let's meet back here at 1:30.

[Whereupon, at 12:39 p.m., the proceedings were recessed, to be resumed at 1:30 p.m., this same day.]

A F T E R N O O N S E S S I O N

MS. AXELRAD: Tracy.

MS. ROBERTS: We are going to start with Subpart G, Laboratory Controls, 212.60.

If there is any comments on this section, I would like to go over them at this time.

DR. BARRIO: Do you think we could revisit briefly a couple points that we have on the previous sections?

MS. AXELRAD: Sure.

DR. BARRIO: The comments will come from Dennis.

MR. SWANSON: I think a couple things that we summarized from this morning's conversations, we just want to have a record of summary comments. We definitely have concern regarding reserve samples and really can't see the purpose for them, so we suggest that any statements related to reserve samples be removed.

We have a major concern regarding the testing required for the acceptance of components and in-process material. We must definitely make efforts to minimize the testing required when you get a Certificate of Analysis associated with the product. There should be no requirements for additional testing with the emphasis again on end product validation, the quality of your end product.

We would definitely--I think Tracy mentioned this morning about the 483 process especially as this evolves

over time, there is definitely a need to keep I think this committee or some kind of an advisory committee actively working with you in compliance at the FDA to take a look at 483s, so that there is some public input on your evaluation of 483s instead of just your input would be an important point.

I think we have a concern, and this may sort out in later discussions, but how these CGMPs relate to PET drugs as the subject of INDs or RDRCs. Again, we have a lot of questions about as we develop new agents for research, what kinds of product validation, procedure validations are going to be required, and what I think we heard this morning is that there may be quite extensive validation associated with new drugs under development versus drugs we have been involved in, and again, you know, you have developed research agents which may have a very limited application as far as human subjects are concerned.

You may do one research study with a certain agent that involves a maximum of 30 subjects, and to require extensive validation of the process, et cetera, for a research study that involves a limited number of people just doesn't seem to make a lot of sense to us.

Again, I will reemphasize, and I think the committee will reemphasize, there needs to be, and the FDA really needs to think in terms of end product validation,

the emphasis has to be on testing the final product to ensure that it is, in fact, the product that we say it is and has appropriate strength, quality, and purity.

That concept needs to definitely be applied to research agents also.

MS. ROBERTS: I am sure you are not familiar, then, with our INDs and how GMPs apply to them in normal drug realms, and things like that, so I won't go into that now or how that is done, but for your own peace of mind, you might want to research that so far and see how we deal with that, but we do have policies and procedures of how we normally do that.

I think a lot of what you are fearing, we don't normally look at for an IND anyway during that time, but we can explain that and talk about that at other times, but we do understand what your fear is, but it is not totally founded. We will discuss that and take that into consideration.

Now, we will begin with the Laboratory Control section.

DR. CONTI: 212.60(d). The identity, purity and quality of reagents, et cetera, must be adequately controlled. Maybe it's just me, but what do you mean by "controlled" in this context, since we have little to say about many of these issues?

DR. KASLIWAL: In the solutions that you prepare, you will label them with the correct label, you know, identifying what the composition is, the reagents that you use, you will specify their quality, and that is what you will stick with

DR. CONTI: Am I safe to say cataloged is a better word as opposed to controlled? Maybe I am just misunderstanding the language.

DR. KASLIWAL: For example, if you specify for a reagent ACS grade, that means that is what you will use, and, you know, actively, that is what you will use, you control that at that level.

If you specify certain grades, that is what you will use to control it.

DR. CONTI: So, it is really the specifications.

DR. KASLIWAL: You can take it out of COA, yes.

MS. ROBERTS: In addition, what is also covered under this Subpart (d), when we talk about reagents, solutions and supplies used in testing must be adequately controlled.

If for any reason, for example, the media used in the sterility tests, that is one example that we could use, that you need to do growth promotion on the media to make sure that it is going to work. You have an adequate control over the way you have stored it, so it doesn't deteriorate.

Those are the fundamental purposes behind this, as well as the solutions that you make, that the reagents or the supplies that you use in some of the testing are actually part of the validation of that test, and that you are controlling those things.

DR. CALLAHAN: Regarding the growth promotion, once again, that would be something that could be done by the provider of the medium, and not in your own laboratory, correct?

MS. ROBERTS: It depends on how you store it and what you do with it. Sometimes inherently in the sterility tests, there is a growth promotion, and there is a built-in validation that you should be doing, and that is what is meant by that also.

DR. CALLAHAN: Right. Regarding the sterility issue, David Hussong and I put together that piece of the USP chapter, and there was a mention earlier that something very much like that would be included in the guidance for the sterility testing.

I don't think there would be individual growth promotion tests performed on site. I think that was something that was referred to through a certificate from the manufacturer.

MS. ROBERTS: That is just one example that I could think of off the top of my head, but in the guidance

document there will be more examples of what we mean. However, that is like the blanket statement that would cover reagents or supplies that could be expected to have some kind of deleterious effect or if you don't control them per se, either temperature control, that is what is meant by this point.

MS. AXELRAD: I should mention that we have put out over there a piece entitled, "Microbiological Validation of Sterilization, Sterility Assurance," attachment to an application for FDG F 18 that describes how this issue would be addressed. It is sort of an addendum to the model chemistry thing that deals with sterility.

Unfortunately, the person who was here, there was somebody here this morning, Paul Stinavage was going to address it, but he had to leave, so we didn't get to that. But anyway, you should know it is over there and get a copy of it.

DR. CONTI: Section 212.60(b). Two comments. One is I assume this will be in the guidance, but "scientifically sound sampling" needs to be defined someplace along the line.

Then, there is a qualifier at the end of that, "when such standards exist." Is there a guidance or some sort of comment on when they don't exist as to what to do?

MS. AXELRAD: That phrase just relates back to

when there are standards for identity, strength, quality, and purity. That is what you are testing against if there are such standards, and if there are not, then, the correct wording is conform to appropriate standards, whatever they may be, whatever it is that you think is appropriate for the particular drug product or thing that you are testing.

DR. CONTI: So appropriate standards could be defined by the applicant then.

MS. AXELRAD: Yes, although if there are existing standards of identify, strength, quality, and purity, they have to meet those.

DR. KASLIWAL: A lot of these standards are probably going to be defined in your application, so for components and container-closures, it was finished product.

DR. CONTI: How long do we keep these records for?

MS. ROBERTS: That is in the record section, three years.

DR. CONTI: Oh, three years, I am sorry.

MS. ROBERTS: Are there any other comments specifically in this section?

MR. SWANSON: Under (g) and (g)(1), "Each laboratory performing tests related to the production of a PET drug product must keep complete records of all tests necessary to ensure compliance with established specifications and standards, including examinations and

assays, as follows:

"(1) A description of the sample received for testing including its source, batch or lot number, date and time the sample was taken, date and time the sample was received for testing, and its quantity."

Most of us do produce like FDG and do QC testing as a contiguous process. I mean it is overkill in documentation to now require us to document the description of the sample received for testing. I understand we produce it and then we test it. We are not sending it somewhere else for testing?

MS. ROBERTS: That could be easily then captured in the procedure that you would have for this, is that will test as per the batch record. We are testing the whole sample that we produce. But I think the important part here also is the date and the time the sample was taken, and I would assume that when your QC is testing the sample, don't they write on the results the batch or lot number, the date and the time that it was tested? That is what is meant by that.

MR. SWANSON: It's all part of our batch record. It is one contiguous batch record.

MS. ROBERTS: That would meet the requirement then. We are not asking for separate pieces of paper. If there is other means to meet the requirement, if you are

saying it is contiguous and it is in the batch record, that would meet this requirement.

MS. AXELRAD: If the batch record has a step in it that says, okay, and after you have filled the vial or whatever, you pull out some and you do the following tests on it, and then your batch record reflects it for batch number, you know, 222, you pull the sample and you did the tests on it, that is all you have to do.

MR. SWANSON: As part of the contiguous process, I don't record the date and time I took the sample, I don't record the date and time I received the sample. We are just doing it, okay.

MS. AXELRAD: But there just has to be some record for somebody who comes back to see if you have actually been doing it, to verify that, in fact, for each batch it was done. We can work on the wording, but that is the idea. I mean you have to have a record. You can't just say, oh, well, we are supposed to do it, and therefore we must have done it.

MR. SWANSON: I don't have a problem with documenting. What I have a problem is over-documentation of things as now required by your regulatory wording here.

DR. KASLIWAL: I think the intent is that, for example, at the end of synthesis, you are going to do an assay, so you have to have a calibration time there, so you

will have that in there someplace, things like that, and then when you testing is finished, what was the end of synthesis time, and things like that. We will look at the wording there.

DR. CALLAHAN: You have the data for the test result, so that suggests it was done, so just saying that you do it doesn't add much to it since the blank for the test results, there is data there.

MS. ROBERTS: It is important in the batch record, then, you are going to include this, it is part of the batch record and that on your results that you get, that you are printing out, there is identification of what test result that is for, which particular batch it is for, what size sample you use. That is what we are asking for, is that on the actual laboratory results, there is identification, so that we know what the sample is that you were testing.

DR. BARRIO: In the same section, (g)(1), what do you mean by "quantity"? Many times we have no idea how much. Do you mean volume, activity?

DR. KASLIWAL: Volume, I would think because especially if you are making your batch in a vial, in the model application, I would think you would specify, for example, you take a mL out, whatever volume that you take out for QC testing, so that volume you took out, you would specify you took out that volume.

MR. SWANSON: But you are not talking about getting down to the level of the volume that I spot on the TLC strip.

DR. BARRIO: No, no.

MR. SWANSON: That is what it says.

MS. ROBERTS: What is the quantity of the sample you took to do that specific test, was it a mL, was it one vial, was it--

DR. BARRIO: I think it refers to the quantity of the sample received for testing in general, right? This is my understanding. Is it right?

MS. ROBERTS: Yes.

MR. FERRIS: In other words, the sample used that is extracted from the batch that is used for quality control testing may very well be used--you would run several tests on portions of that sample. You want how much was taken for quality control testing, period.

MS. ROBERTS: Yes.

DR. KASLIWAL: And the model application, you would describe how it is distributed among individual tests.

MR. SWANSON: I am back to the same issue. You want me to record a volume for a drop I put on pH paper, you want me to record a volume for a drop I put on the TLC strip? That is the way this reads, and that is what we are hearing from you, and that is kind of absurd.

MS. ROBERTS: What this really refers to is if you have a separate quality control unit, you are taking a sample, you are sending it to them a different unit where you are kind of losing your control, they are receiving the sample in.

This is when this documentation comes into effect, how much of the sample they received from you, the date and the time that it was received, the batch, the lot number. That is what this number 1 refers to.

If you are taking that sample out, you are sending it to your QC lab, they have to document when they received the sample, the date, the time, the quantity that they received, so that you have a control over where those portions of the sample went. That is what is specifically meant by this.

MR. SWANSON: And as I said, that is not applicable to the way most places do it, which is as a contiguous process. I understand where you are coming from, but the way this currently reads is everybody would have to do this, okay. So, you need some additional wording to somehow indicate that if you are transferring a sample to a separate testing facility or unit.

MS. ROBERTS: That will be made clear.

DR. CONTI: No. (2) specifically says used for each test, so that is the issue, I think.

MS. ROBERTS: In (2), if you need one mL to do a certain test, we would expect that you are always going to use the 1 mL. It's our way of, you know, why did you take 2 mL at this time, why did you only use a drop this time, if your test method calls for a specific quantity. That is what this is in reference to.

DR. BARRIO: The next item is (g)(2), mentioned or determined by your chemical purity, why is it important to weigh the sample under (2), "statement of the weight or measure of the sample used for each test," because it's a relative term, of course, relative by your chemical purity, chemical purity, or solvent percentage, whatever it is.

MS. ROBERTS: This particular section of the regulation for laboratory control is the blanket for all tests that you could possibly do under this, not just specifically for radiochemical purity, a sterility test. This is just the basic documentation that we expect to see when we come in and that we think it is necessary for you to have.

Like I explained, No. 1 is when somebody receives the sample, they have to document what they have received, a weight, a measure, the size, physically identifying it, so they can tell you what they have received.

No. 2 is when you do, when you are actually doing the test on the actual raw data that you are getting. We

expect that there is a description of the method that you are using whichever method. It could be a number, it can refer back to the USP, a record of all the calculations performed, whatever you did in hand, we want to see that, and then a statement of whatever size of the sample that you tested, whether it's a weight, a measure, a milliliter, a drop, whatever that method that calls for, we want to know how big was the sample size, if it is relevant of course.

DR. KASLIWAL: Another thing, it is a vague "or measure." A measure could be CPMs.

DR. BARRIO: It doesn't make any difference provided that you are within the limit of sensitivity of your procedure. You are looking at relative terms.

DR. KASLIWAL: That is the idea, that you putting a certain limit of detection, that you are able to pick that up.

DR. BARRIO: You have to remember though, Ravi, that every time we take extra time to measure, weigh, or whatever the sample, this sample is frequently radioactive, then, we don't want to necessarily expose people to radioactivity when these procedures are not really fundamental for the tests we are going to perform. That is the point we are making.

MS. ROBERTS: Then, how do you know how much of the sample you need in order to test it?

DR. BARRIO: It's in your procedure. You have a procedure that says in order to test this solvent, whatever the solvent may be, then I inject in my HPLC so many microliters, but you need to know the volume you left behind.

MS. ROBERTS: Oh, no, that is not what we are asking for. We are asking for the amount that you are required to inject.

DR. BARRIO: It's in the procedure. It will tell you how much you inject.

DR. HOUN: This is the description of each method.

DR. BARRIO: Right.

DR. HOUN: A statement of weight or measure would be in that description.

DR. BARRIO: Barrio.

DR. HOUN: It is not saying at each time you must measure and write it down.

DR. BARRIO: Thank you, Florence.

DR. CONTI: Can I go on to 212.61? Under the Section (a), I have a question about whether or not we have to account for what a distributor may do with the manufactured vial.

We may be able to do a stability study at room temperatures in our hood over a period of time, but obviously, a shipped vial undergoes different environmental

challenges between the time it has left the manufacturing facility to the time it is injected into the patient, and that theoretically would fall under the jurisdiction of the state boards of pharmacy.

So, how do we reconcile this?

MS. ROBERTS: The way that I envision this to be done is you make the product and you need to ship it somewhere to the receiving facility. Whoever happens to be the receiving facility, before you release that product, it is still technically in your possession, and you must control what happens to that product.

You are responsible for the fluctuations in temperature or making sure that you know what that is or putting on the carton that it must be shipped within a certain temperature, because you only have stability for it within that temperature range.

DR. KASLIWAL: I think what you would do is when you ship it out, you put a time or, for example, let's say eight hours from time of calibration, your product expires, and as a manufacturer, that is what you need to validate that for eight hours to support that label that your product is good.

DR. CONTI: What I am saying is to do the testing, I can keep that for eight hours in my hood, as a vial, and do the stability testing, during that eight-hour period it's

fine, and so that's the standard. But what happens when I ship it to a distributor in the first hours, there are seven more hours to go, and that vial undergoes all kinds of transportation. It is not in my hands, it is not in my control any longer, yet it's in that expiration time?

DR. KASLIWAL: The way manufacturers cover themselves with that is they do testing under accelerated conditions, elevated temperatures.

DR. CONTI: So, it's not really suitable, it's extremes we have to actually do.

DR. KASLIWAL: You can do that if you want to label, let's say, 15 to 30, then do extremes. In the USP currently, what we recommend if 25 degrees plus or minus 2, or if you want a 30 degree, it has to do with the label, and then accelerated 15 degrees higher above that at 40 degrees, but we are not requiring accelerated conditions for these drugs.

MS. ROBERTS: Did we adequately answer your question?

DR. CONTI: I am just concerned that if a vial of FDG is sitting out in the sun somewhere and gets hot, and suppose that other temperature range of what our expiration criteria are going to be tested within, and then all of a sudden, something goes wrong with that product, we are responsible for it, yet, it was the distributor who

mishandled the product.

MS. AXELRAD: But you are responsible to the extent that you need to put on the label what the conditions are of storage. If you put on it certain conditions, and you have justified those conditions by doing stability testing, you don't have any control over what they do with it, and nobody is going to hold you accountable for that.

The idea, though, is to establish storage conditions and give directions to the people who are going to be handling it to make sure that that doesn't go out of spec.

DR. CONTI: I don't have a problem with that.

MS. AXELRAD: And that is no different than a regular pharmaceutical that is given a two-year or whatever expiration date, and then shipped through multiple hands on trucks and whatever and ends up on the pharmacist's shelf.

We are not going to hold the person accountable for what happens all in between, but we are going to make sure that when they establish the two-year expiry date, that they have a basis for testing it under reasonable conditions to make sure that it isn't going to just easily lose potency or whatever.

MR. FERRIS: So, you anticipate basically that most stability studies will be done at ambient room.

DR. KASLIWAL: The other precautions that you can

take is there are a lot of indicators you can put on the box that will tell you if you exceeded temperatures significantly.

MR. KUHS: Is this something that you have to do periodically, in other words, how often does this need to be done if we are talking about different conditions that may exist for shipping, in other words, if you are shipping in Arizona where your storage conditions might well exceed 40 degrees and where it is likely that the container would be tipped upside down at one point or you are expecting that stability studies would be done in an upside-down vial as well as a right side up vial, and at extreme storage conditions?

DR. KASLIWAL: The model application, yes, we require that it be done upside-down bottle at least the stability batches, and what we require is if your proposed drug for these three drugs is within the strength of reference listed drug one batch at the time of submission, and a minimum of one batch per year after that.

But if it is a higher strength rather than the reference listed drug at the time of submission, three batches at the highest rate of concentration, and again a minimum of one batch per year.

MS. ROBERTS: I see that we have moved into the next section on stability. Are there any other questions or

comments under stability?

DR. HUNG: Section 212.60, Subsection (d). I believe the proper labeling for the solutions you have expiration date included.

MR. CHALY: Thomas Chaly from North Shore University Hospital.

Regarding the testing, for seven pharmaceuticals we take less than a drop of sample to do TLC testing, and there is no way that we can record how many mL we took for those testing. We have already written in our procedure that at the end of the synthesis, for example, in the case of FDG, we take 10 microcurie of the sample or 10 mL of the sample, and do the testing like that.

MS. AXELRAD: I think that is what we just said, that that's fine, if your procedure says that is what you do, that is all this means is that you are supposed to describe the method. By saying that the method says take 10 whatever and inject it, that's it. That meets this requirement.

MR. CHALY: But we are afraid that if this kind of wording is there, the inspector comes, and we will be in trouble at that point.

MS. AXELRAD: We are going to train the inspectors, so that they know what to look for.

MS. ROBERTS: We will move on to Subpart H,

Finished Drug Product Controls and Acceptance Criteria, 212.70.

DR. CALLAHAN: I just have a comment under (a). It says, "For each batch of drug product, you must establish criteria." You is defined actually under the definitions as us, I guess. That seems like we have the ability to set the standards for strength, quality, purity, et cetera, as opposed to someone like the USP.

So, could we set our own standards for the quality, strength, purity, or do we say that we are going to comply with USP or do we have an option to say something else?

MS. ROBERTS: With any product that you put an application in for, you have the option of whether you are going to follow the USP monograph in which it is usually labeled as USP, which means you will comply with all the specifications in the USP monograph.

You also have the option to determine your own specifications for your own product that you develop, and that goes through the review process.

DR. CALLAHAN: That means for a product that is not in the USP or can that be for a product that is listed? You are saying we can set a different set of standards for a product that is listed in the USP?

DR. KASLIWAL: Right, yes, you can submit in your

application a different method of testing or if that is what you are implying. Our view is that USP is the minimum standard for us, and whatever else you want to go from there. That will be on an individual basis in your application.

MS. ROBERTS: And if your standards are different than the USP, you just can't label it as a USP product or claim it's USP.

MR. SWANSON: Along the same line, under (c) it says, "You must conduct laboratory testing to demonstrate that each PET drug product meets acceptance criteria before release. You must establish and document the accuracy, sensitivity, specificity, and reproducibility of the test methods."

If I am using USP test methods, am I required to do all of this documenting the accuracy, sensitivity, specificity, and reproducibility?

MS. ROBERTS: Only to the extent that the USP methods are usually you would have to show that they work in your facility under your establishment with the equipment that you are using. There wouldn't be a full method validation per se if it's in the USP, however, you would need to do like a qualification to show that you are able to test this product in your facility using the USP method.

MR. SWANSON: So, tell me for a TLC test, give me

the specifics of what you would be looking for.

MS. ROBERTS: I can't give you the specifics right now, at this time. I would have to look to the USP and sit down and look at that. However, in the USP, there are sections that require you to do the accuracy, sensitivity, specificity, and reproducibility of at least HPLC method and the chromatographic. It is built into the USP.

DR. BARRIO: Then, you mean if we use a USP procedure, we have to do all this, right? What would be sufficient information to satisfy that requirement?

MS. ROBERTS: I can't answer that exactly without having the USP in front of me, but within the USP, under HPLC methods, there is a section, I believe, that speaks to making sure that it's accurate reproducibility, there are system suitability tests that need to be done if you are going to use those USP methods.

DR. BARRIO: Then, this is going to be the standard.

MS. ROBERTS: That would be adequate if you are doing the USP method as long as you are following all of the USP validations that are required.

DR. KASLIWAL: I think you probably need to do some validation of the USP method, but it depends what it is that you are doing. A lot of people don't always use the method that was used in the USP, so the impurities and other

materials may be different depending. So, whether your method still holds or not, you need to validate that.

Sometimes the USP methods, you know, and that is assuming that the USP method was validated to begin with, hopefully, USP will have that validation information, but assuming it is validated, you may have to do some minimum validation depending on your conditions of use, for example, let's say TLC method, you spotted so many counts, and you have certain sensitivity that you want to get to be able to pick up some other materials, so you have to validate that you can pick up that amount of material.

For example, GC, you may have a specification set over here, but your working levels are way down here, and that is where you see materials, but since your specifications are set way up here, you are going to have to demonstrate that the method is good from here to there, is it linear or not. Otherwise, it is very difficult to accept whether those specifications, you are going to still pick up those amounts accurately by those methods.

DR. BARRIO: But the USP established that. We have done these with all the procedures I guess for everyone I believe. If it is explicitly indicated, should we redo it again. You are saying yes.

DR. KASLIWAL: You may or may not depending on what validation USP has, and when the question comes, we

always go up to USP and we do ask them that we want to take a look at their validation file, and they do comply with that.

DR. CALLAHAN: Can we go back up to (a) for a moment, 212.70(a)? Just a point of clarification, "to ensure that each batch of PET drug...before it is released." In the case of ammonia, it is a sub-batch or some test batch that we run first, whatever we call that.

Again, we are getting back to the terminology, but the point is that there will be a sample of drug that is tested, then, a series of samples will be used, and so it is not actually each batch.

MS. ROBERTS: I think what we discussed at the last meeting was that it was described to us that technically, it is a whole batch, and that is where there is this sub-batch came in.

DR. CALLAHAN: Okay. So, by testing the first one, we have met this criteria.

MS. ROBERTS: By testing the first one and then some middle or the end, or whichever you had described, and we had agreed that that would constitute the testing of the batch.

DR. CALLAHAN: And pyrogens are not included here because they are not a release test, is that true? It said pyrogens do not have to be determined prior to release, is

that true?

MS. ROBERTS: Yes, that would be true. The sterility test is the only one that doesn't need to be completed prior to release.

DR. CALLAHAN: I think in the application, pyrogens, it is stated don't have to be done prior to release.

MS. ROBERTS: Is that for every PET drug product? I am sure the LAL test takes 60 minutes, and in other circumstances, it can even be validated for a shorter time period.

DR. CALLAHAN: Pyrogens are not included in 212.70(a).

MS. AXELRAD: We could correct that.

DR. CALLAHAN: In the application, it is stated that it is not a release criteria for FDG, for example.

DR. KASLIWAL: I think basically, on that, the working philosophy, having talked to David Hussong, who has worked on that, we will probably more than likely follow what agreements we reach with USP on that and the component chapter.

DR. BARRIO: On the same page, (d), when we say, "You must establish and follow procedures to ensure," et cetera, (d)(2), for short-life nuclei, for ammonia, that may be a deadly requirement.

MS. ROBERTS: The intent of this purpose was to make sure that even though the laboratory testing was done, that the calculations are checked, it is reviewed, and indeed it is correct testing, everything was running the way it should be, now, you are saying for which product would it be a problem?

DR. BARRIO: O 15, N 13.

MS. ROBERTS: I think there might be in some instances.

DR. KASLIWAL: Let me ask you this. When you are making this quality control, initial quality control lot batch, a sub-portion or whatever, so you are not completing the testing before you start making your regular batches.

DR. BARRIO: Well, we have requirements or we indicate which are the appropriate laboratory testing, that is under (1), for the different nuclei.

I am referring to (2) that goes beyond that, associated laboratory data, and this may be truly impractical. I am not sure what you are referring to beyond the laboratory testing, but, you know, it may be difficult to do that.

MS. ROBERTS: How long would it take, what do you do now with respect to reviewing laboratory data, does anybody review it, or does just the person that does the test, and then it is never looked at again?

DR. BARRIO: In general, the laboratory testing the quality control is the trigger for release if the product is appropriate and meets the standards, we just go ahead and send it out.

MS. ROBERTS: It never gets a second review to make sure the calculations are correct or the right method was used or anything to that effect?

DR. BARRIO: The HPLC or GLC will tell you right away whether you have impurities or not. I mean you don't have to wait too much.

DR. CONTI: In addition, you can take this to the extreme and say associated laboratory data could be the documentation of the HPLC fidelity and quality control, and the starting materials--I mean you can go on and on. I mean how many things do you want to review before you release the product.

I think Jorge's point is that if the laboratory testing is appropriate, that is the release criteria, period, and you can retrospectively review things, but I think particularly with short-lived isotopes, it doesn't make any sense to do this.

MS. ROBERTS: And then what happens for these products that you review them at a later date and find out that there was a problem? They are already gone.

DR. CONTI: Your laboratory testing has already

been completed, and it met the release criteria.

MS. KEPPLER: I think we are talking about two different things. I think that Jorge is looking at the laboratory testing is completed, means that he looks at the results of the HPLC printout and evaluates it and says it is good. I think that is what you mean by saying that you are reviewing the laboratory data.

It is not like he is injecting his sample into the HPLC, doesn't look at the results, but releases the product.

I mean do you mean by the fact that your data is reviewed, just looking at the results of that test and seeing that indeed it is water?

MS. ROBERTS: No. What is meant by this is that you are going to review the laboratory data, the HPLC chromatograms, they are signed off on, everything is okay, it wasn't done off-line, all your calculations are correct, and that is indeed the answer that you should get, and I think I am hearing that that never gets done here.

DR. CONTI: I guess the issue is in the language as usual. The appropriate laboratory testing is completed and reviewed might be a way of putting it, such that you check the results to make sure they make sense before you release the product, and then any associated laboratory data that may be related to quality control procedures or other things could be reviewed retrospectively or just this thing

just deleted.

MS. ROBERTS: So, you suggest that as a quality control function, they would look at this data after the product is already gone other than like looking at all the HPLC chromatograms or calculations that would need to be done?

DR. CONTI: Again, I think the testing that we are doing is such that you can look at it and see if it makes sense in a very short time frame without sitting there and checking the calibration of the HPLC and doing the other quality control tests associated with this.

MS. ROBERTS: Maybe we are misunderstanding each other. I don't mean all of the quality control tests. I mean you test the product, you get an answer. You have that answer, and then there was documentation to get there, not related to the calibration of the machine, just related to the actual tests, maybe looking at a peak height or making sure there is not other impurity.

I think that is what you mean by makes sense?

DR. CONTI: Right, that the RF on the TLC is where it should be, that is the end of it. You don't need to do anything more with it. That is an instantaneous determination when you do the test.

I guess I don't know what review means here.

DR. BARRIO: I think that is a problem as

suggested by Peter, would be testing is completed and reviewed or analyzed, I don't know, something simple.

DR. CONTI: And noted.

DR. BARRIO: Or noted.

MS. ROBERTS: I think we are on the same page. It is just kind of the words, and I will try to work on that.

Is there any issue with the authorization by dated signature?

DR. CONTI: That could be a scribble on the HPLC.

MS. ROBERTS: Acknowledging that the test was completed and acceptable.

DR. CALLAHAN: That would be for each test or the signing off for the release on the batch record.

MS. ROBERTS: It says for the release.

MR. CHALY: For the quality control thing, for example, when you take FDG after the preparation, we take a sample, we inject it into the HPLC, we see the peaks coming out, and depending on the ratio of the peak, whether it is 95 percent pure or 99 percent pure, that is recorded in the batch sheet, and based on that one, will release the sample and we say that this compound is good for patient use. That's the way we do. We don't call anybody else to look at it because we know if it is not good, we are not going to release it.

These are the standard values, 95 percent or 98

percent or 99 percent.

MS. ROBERTS: Thanks. I think that is what I really meant here. It's just a bunch of extra words.

MR. SWANSON: A couple quick comments under (b), "Sterility testing need not be completed before release but must be started as soon as possible," I think USP says within 24 hours because of radiation safety considerations associated with sterility testing, so there is inconsistency between here and what we are seeing in the USP guidelines.

If you go down to (d)(3), "Release is authorized by the dated signature of a designated, qualified individual." Your previous requirements say it has to be by somebody from the Quality Control Unit or person, so you need to say release is authorized by the dated signature of the designated Quality Control Unit or person.

MS. AXELRAD: What are you referring to as the previous? You want it to say that?

MR. SWANSON: Say what?

MS. AXELRAD: You want it to say release is authorized by the dated signature of a designated qualified individual from the Quality Control?

MR. SWANSON: I think your previous statement said that only the Quality Control Unit can authorize release.

MS. AXELRAD: What previous statement?

MR. SWANSON: In this document.

MS. AXELRAD: I don't see that in here.

DR. HOUN: We can take a look at that again.

MS. AXELRAD: We can look at it. I think we were again dealing with the issue, the suggestion that we were requiring two people, and we were trying to eliminate that wherever possible, so we just said release is authorized by the signature of a designated qualified individual. We weren't saying that you had to have a separate person do it.

DR. HOUN: I just want to get the ICP's comment on (b) in terms of if there is a sterility problem, a notification of the doctor who wrote the prescription, is this acceptable?

DR. CALLAHAN: In the case when that product is distributed to a nuclear pharmacy for subsequent dispensing on prescription, it might be adequate for the PET drug producer to notify their pharmacy, because the manufacturer/producer wouldn't necessarily know the prescribing physicians nor the patient.

DR. HOUN: So, in cases where the product is released to a pharmacy, the notification would be to the pharmacy--to the receiving unit.

DR. CALLAHAN: Right, that language would cover it all, if it was the clinic or if it was the pharmacy, even though we don't describe a receiving unit as a pharmacy, I don't believe, maybe we should.

DR. HOUN: And in the case where you have a smaller operation where the receiving unit is actually--

DR. CALLAHAN: Upstairs.

DR. HOUN: --or you are directly doing this into a patient.

DR. CALLAHAN: Well, then, we would have that data, and we could contact the referring physician.

DR. HOUN: Maybe that could be put in guidance in terms of who the appropriate receiving--

DR. CALLAHAN: But just denote that there are some cases where the manufacturer would not have that information available to him.

MR. FERRIS: That notification, as it is written here, happens if there is a sterility positive, and you are saying even without investigation. My point is, is suppose it is anasterile that is causing contamination, are we notifying the physician that there is a sterility failure or that there is a potential sterility failure?

MS. ROBERTS: What is intended by this is a true sterility test failure. We wanted to waste time, however, if it is the laboratory's fault, we wouldn't want to unduly alarm the receiving facility either, but I can see a problem in the case where if it is taking the laboratory a week to do the investigation, I would find that a problem, if it takes that long to notify them of a sterility test failure

after you have figured it out.

This is what is envisioned, is that if there is an initial sterility test failure, it triggers some kind of investigation, and then it is determined whether--if you can rule out the laboratory or if it is clearly the laboratory's fault, that is easy enough, it is not a true product failure, however, if the investigation isn't sure right away, I would assume that you would notify them of the potential then or the actual sterility test failure, because I would hate for you to wait two more weeks for them to retest and especially since you are not keeping or you don't want to keep retains.

So, that would be troublesome to try to do a retest if you cannot duly rule out a product sterility failure by a true laboratory error, you should notify them as soon as possible.

DR. HOUN: And I think probably in guidance, we can describe what does immediately mean or with some assurance. I don't think we should put it in the regulation 24 hours or 12 hours or whatever.

DR. HUNG: What happens if the failed product, the failed sterility test has been injected into a patient, should the patient be informed by the prescribing physician, and if so, what sort of a time period?

MS. AXELRAD: Well, we were just suggesting that

the physician ought to be notified, but the comment we just got back was that we shouldn't notify the physician, we should only notify the pharmacy who received it.

I guess I would wonder since sterility test failures are supposed to be incredibly rare and very unusual events, and since that is probably the single most significant failure you could have in one of these products that would actually affect a patient, who would have already gotten it two weeks ago, that perhaps notifying the physician in these very unusual circumstances, and perhaps even the patient, might be appropriate.

DR. CALLAHAN: What I suggested was that the manufacturer may not have access to that information. That is why we notify the pharmacy. If the physician is available to us, we would notify the physician. However, I don't think we would directly notify a patient. That is the physician's prerogative based on his clinical judgment of the patient's condition, what the risks are, and so it is not appropriate for us to contact patients.

MS. AXELRAD: But you could probably get the name of the physician from the pharmacist and make sure that that notification is made to the physician.

DR. CALLAHAN: Again, we are crossing this line that we want to draw somewhere.

MR. SWANSON: When you have a product failure with

a traditional drug, do you require the traditional drug manufacturer to go out and identify each physician that wrote a prescription for that drug? Of course, you don't.

MS. ROBERTS: The requirement as it reads here in the regulation is to notify the receiving facility as soon as possible, immediately, and the physician if you know who the physician is.

DR. CALLAHAN: That's fine.

MS. ROBERTS: Are there any additional comments on this section?

MR. SWANSON: But that is not what that says, though, so be aware of that.

MS. AXELRAD: Right, but on the one hand, you are arguing that you are not like manufacturers, that you really more like small operations in the practice of pharmacy, but then you are now arguing that, you know, well, manufacturers aren't required to notify the physician or the patient, why should we.

MR. KUHS: I think there needs to be a clarification of the receiving unit, and the receiving unit could be a pharmacy, in which case you would not know some of the end users. The receiving unit could be a physician in which case you would document that, and you would notify him. I don't think they are mutually exclusive of one another. We are not saying we will do one and not the

other. It's that you use the distinction based on where you distributed it to.

DR. CALLAHAN: You can only act on the information that you have in hand, and it may be impossible to gather beyond a certain level. What's all we are trying to say.

MR. SWANSON: Fundamentally, in response to what you just said, we are conceding the fact you are going to regulate us as a manufacturer. That doesn't entitle for you to regulate us as both. Okay?

MS. ROBERTS: Are there any more comments under that section, under Controls and Acceptance Criteria?

Then, we will move on to 212.71, What other actions must I take if a batch of PET drug products does not meet the acceptance criteria?

DR. CONTI: In regard to complaints, if it hasn't met acceptance criteria, would it have been released in the first place unless I guess there is potentially a test that would be done retrospectively, but I am reading this as acceptance criteria for release, and in which case, why would--I mean I guess our distributor might complain that they didn't get the vial, but what are you referring to here as far as complaints are concerned?

MS. ROBERTS: Where are you reading?

DR. CONTI: 212.71(a).

MS. ROBERTS: Oh, what this means is that when you

are doing an investigation of a failed drug product, you are required under these regulations to keep complaint files for the specific drug product. We would expect that an investigation would include a review of your complaint file for that drug product, not for that particular batch, but for the drug product as a whole.

MS. KEPPLER: And this would be I think, Peter, not if they released it, this would be for probably unreleased product, you know, you had a run failure, you should keep track of run failures, investigate the causes.

Is that the purpose of this?

MS. ROBERTS: That is the purpose of that. Also, we ask that if you do have a run failure, that you look back at product complaints to see if you started to have a problem maybe and that is evident by complaints, you might never have a complaint, and then that will be easy, but if you do have complaints, you should see maybe if it is attributable to this same problem that you had that the batch failed.

Are there any other comments or can we move on to Labeling and Packaging?

MR. CLANTON: Jeff Clanton, Vanderbilt University.

I don't see where this particular section allows for distribution pre-release, which is a common practice.

MS. ROBERTS: I don't understand what you mean by

pre-release.

MR. CLANTON: In other words, the material has gone through the production cycle, it is packaged for shipment in interstate commerce, it is shipped, and the QC is ongoing during the process of while it is in transit.

MS. ROBERTS: We discussed that earlier, and we have made a distinction between distribution and release. You are allowed to put the product into distribution prior to release. You just cannot administer it to a human prior to release.

MR. CLANTON: I just didn't see in the section where it allows that, though.

MS. AXELRAD: I think it is under Distribution, 212.90. "You must establish, maintain, and follow procedures for the control of distribution to ensure that only those products approved for release are used, and that the process of shipping will not"--I mean that is just one of the places, but that is where it really appears I mean other earlier section.

MR. SWANSON: Under (b), the date and time it was prepared, do you really mean date and time of calibration? Prepared is when do I start that.

MR. FERRIS: And why use that on the label? It should be calibration time.

MR. SWANSON: It should be calibration time, I

think. Probably in your guidance document, you are going to have to address, do you mean in the label affixed to the actual immediate container of the drug or the shielding of the drug? For example, you require strength, okay, and strength is something is we determine at assay, and if we have to put that label on that vial, that is a fairly significant radiation dose. So, that is one where you may want the strength to appear on the lead shield associated with the product.

DR. KASLIWAL: Some people use the strength test.

MS. ROBERTS: Any other comments on labeling?

MR. FERRIS: On (d), when you say "labeling and packaging operations must be controlled," I would like to get a sense of--to me, that means reconciliation, label reconciliation. Ultimately, a label is issued, counted.

MS. ROBERTS: That is not the intent here because we understand that a lot of times you just handwrite out a label and slap it on the bottle.

This is meant--and it will be covered also in the guidance--that if your operation is large enough where you are using preprinted labels for what you are doing, then, it is more of a labeling reconciliation control, but for the purposes of what I think the PET center operations are here, this would also cover, if they are handwriting them all beforehand, they are not going to be mixed up. There is

some way to prevent that.

Now, if you are just writing one label and sticking it on the bottle, there is really no possibility for a mixup, so that would cover it.

MR. FERRIS: So, that is going to be applied in a variable way depending upon the scope.

MS. ROBERTS: Yes, depending on the scope of the operation.

If there is no other comments on labeling, I think we covered distribution earlier. Are there any other comments on 212.90, Distribution?

MR. SWANSON: The only comment that I would have would be under (b)(2). Again the patient's prescription, if applicable, or any control numbers is not within your purview.

MS. ROBERTS: Okay.

We will move on to Subpart K, Complaint Handling, 212.100.

MR. FERRIS: Could we go back to 212.90(a). You have that "prescriptions are reviewed to assure that they have been properly filled."

MS. AXELRAD: We already took that out per this morning's comment.

MS. ROBERTS: Complaints? I meant Complaint section. I think we are all starting to fall asleep here

and we still have a lot more to cover.

MS. AXELRAD: One page.

MS. ROBERTS: No, not this. If you don't have any comments on complaints, we will move on to Records, Subpart L, 212.110.

DR. HUNG: Do you accept computer records?

MS. ROBERTS: We have a whole regulation that covers computer records, and that is across every center. That is our Part 11 on Electronic Signatures and also on all Electronic Records. If you wanted to keep electronic records, you would have to comply with that Part 11.

MS. AXELRAD: Are you planning on giving us written comments? We have indicated that we will accept written comments on this preliminary, sort of unofficial draft on or before October 13th is what we said in the notice. So, we will take into account everything that was said at the meeting on the draft and anything that is submitted to us in writing before that date, and we will go back and work on this some more.

MR. KUHS: I think there is one specific charge of drafting a statement on the end of the end of manufacturing process and dispensing under practice of pharmacy and medicine. I think there is a lot of room for clarification on that issue.

DR. HOUN: And any other specific revisions, the

more specific you are in terms of wording, the closer we will get.

MS. AXELRAD: Why don't we open it up to the audience.

MR. CHALY: How long do we have to keep cards?

MS. AXELRAD: October 13th.

MR. CHALY: No, how long all the records are maintained in the PET centers.

MS. AXELRAD: Three years.

MR. MOCK: One very specific question. With all the different QC testing that is required, what happens if my GC column, capillary column used for doing residual solvents or whatever happens to break or the computer fails and the piece of equipment doesn't work that particular day, yet, my track records shows that I haven't had any problem at all with this particular test, can I still release the sample for use because I am not going to get that GC fixed until tomorrow maybe or next week or when the new part comes in?

That might be the place where we can keep a residual sample to do some of these tests after the fact, but I am just concerned with all the different documentation, you know, tests that need to be done, if for some reason a device fails, am I shut down for however long it takes to get that GC fixed or the computer that the

software is operating on, the hard drive crashes, and I can't get it fixed immediately, what are the limitations on product release based upon past history?

MS. ROBERTS: None. Skip block testing is not permitted for these drug products. All release criteria must be met prior to release of the drug products.

MR. HAMMES: Dick Hammes, University of Wisconsin.

Just a general comment about the process. I listened to what you had to say about process validation versus end product quality testing, and I think you need to listen to the reality of what kind of resources we have available out there in the smaller institutions just doing our own in-house use.

I can definitively tell you that the University of Wisconsin does not have the resources to do the documentation and validations and everything that you are talking about today. Granted, we may be at the low end of the curve here and you might want to bring us up.

I have been trying to bring us up to that level for 18 years now. We have been making FDG for 18 years. We have never had an adverse event. We have had successful scans clinically, and if this goes through as it is presented today, I fear that our PET center is not going to continue.

MR. BRESLOW: Ken Breslow, PETnet Pharmaceutical

Services.

I see in the proposed GMP two terms, validation and verification, and I am used to thinking in terms of validation and qualification. I am a little puzzled why a new term of verification was introduced when the term that is most widely used, qualification, would be acceptable.

I think the committee and other people in this room have had a hard time understanding what the difference is between validation and qualification, and I will assume that your definition of verification is equivalent to the definition of qualification.

There was discuss earlier about what do I have to validate, what do I have to verify or qualify, and I think an accurate differentiation could be made in considering the USP test methods as valid methods. USP has published them, and therefore they should have on record the validation of those procedures.

If, as a manufacturer, we determine that the USP methods will work for us in evaluating the drug, then, no further validation of the USP method is required, however, we must demonstrate as a manufacturer that the equipment and personnel that are being employed in the testing of the final product according to the USP validated procedure is qualified to perform that validated test.

Here is where we have to evaluate the sensitivity

and specificity and linearity and reproducibility, and all the same things that we would ordinarily also have to do if we were going to validate a new test method.

MS. ROBERTS: I think I was trying to say that when I was explaining what needed to be done for USP. We are going to look at the terms and reclarify. Verification is listed in the GMP I think once, and so therefore it was defined.

We are going to revisit that to decide what we are talking about on verification and validation, but I don't disagree with what you have been saying about the USP method. I just think there is some different wording in what we have been talking about as what is required.

We are taking that under advisement, and I had addressed that earlier.

MR. BRESLOW: Okay. One last comment on this point.

The valid points that several persons in this room raise as far as the economics and the staffing and equipment availability and the expertise to do some of the equipment qualifications is at the same level as if we were going to validate a test method initially.

I mean the effort that needs to be expended in qualifying the test method, equipment, and personnel is at an equally high level, and the economics behind that is

significant, and the expertise available at many traditional PET sites is lacking because in many instances, you don't have an analytical chemist available at these sites, and are we supposed to go hire analytical chemists who are expert chromatographers that have experience in the GMP regulated industry?

So, I want to reinforce the point that other people made, is that it is a significant and costly exercise.

DR. BARRIO: I would like to address the comment made a minute ago about the possibility of equipment failure. I just say that this is probably a very rare occurrence, but I think the question was very good because that possibility always exists.

One alternative in an emergency situation could be to allow the PET center for this period where this equipment may need to get repaired, is to allow an alternative procedure that may replace, for example, a GC that is not working, another procedure that could allow to have an idea or a good idea of how that radiopharmaceutical is in terms of quality control.

I am not proposing this as a loophole, but rather as an emergency consideration for this kind of situation.

MS. ROBERTS: I don't think that would be a problem as long as long as you are doing a release test for

that specific product, as long as you have thought about from since you have so much history with these drug products and with your equipment, you should know which ones will usually break down, and I would expect that you would have had then, if you are accustomed to this, an alternate method already prepared that you would use in case of an emergency.

DR. CALLAHAN: I don't know of an alternate method for GC for organic solvents, and that is a good example, because that is the only piece of equipment, and in our institution, we do not have a redundancy. I mean it is one unit. I have got six patients upstairs who haven't eaten since 10 o'clock this morning, and they are waiting for their FDG, and I can't do an ethanol concentration because that GC died, and I haven't had an ethanol even approaching the limit for the last 10 years, then, I have real hard time saying that those patients have to go home and not get their diagnostic study and come back some other time.

That is a specific example, and it could be another piece of equipment, but that is a good one because most people don't have a bunch of GCs laying around.

MR. FERRIS: If a trend analysis is done on a periodic basis, one can consider an emergency parametric release.

MS. ROBERTS: Not at this time under these regulations, but we will take it under consideration,

however, there is no provisions for it in this current regulation.

DR. CONTI: But you have an opportunity to write the regulation. Just go ahead and edit.

MS. AXELRAD: We will think about it.

MS. ROBERTS: I just have a question about what happens if there is too much organic solvents in a product, what is the health and safety risk?

DR. CONTI: If your trend analysis says it is unlikely to be occurring is one issue, the likelihood of it being there is very small. These particular solvents, even at these concentrations or even above this, pose very little risk to the patient.

So, even if you put in--I don't remember the exact concentrations, what we actually use in the process--

DR. CALLAHAN: It's 0.4 percent and 0.5 percent for acetonitrile and ethanol respectively, for example, and those are huge. I mean we never approach those kinds of limits. For the ethanol certainly, that is not an issue.

Acetonitrile, again, if you can go up to the level of 0.4 percent acetonitrile in a product and accept it, I mean that suggests that it is not very risky, and the fact that we are down way below that constantly, consistently, to reject an entire batch of material and deprive the patients and inconvenience--it's a case if we were not under the GMP

veil here, we would exercise professional judgment.

I know this is not the arena maybe to discuss professional judgment, but this is the place where I would say that I am releasing this product, and I don't think that I am increasing the risk to my patients whatsoever, and I would go ahead and do that.

MR. FERRIS: Send a sample for analysis later.

DR. CALLAHAN: And whatever else we do, but I mean just at that point, where it is a decision process, you have got to go and decide whether you are going to take care of the patients or not, that is where I would invoke my own professional judgment.

MS. ROBERTS: We take your comments and we will think about it, and we will take what you said, but I just wanted to clarify that parametric release requires a laboratory determination in order to release a product. It's not a skip lot that is the absence of testing.

MR. FERRIS: The laboratory determination I was making there was trend analysis, that's all.

DR. CONTI: The other thing is if you would consider doing this, you may want to include as sort of a mechanism to notify the pharmacy that is receiving the material that this is the case or the physician that is receiving the material that this is the case. Then, it becomes their discretion whether to administer it to the

patient or not.

MR. CHALY: I have a general question. We haven't heard anything, how much we would have to modify our laboratory to come into compliance, because I am very concerned about that one because recently we had to spend about $300,000 to satisfy the New York Environmental Agency for the emission of the radioactive materials, and now we have to spend another $500,000 for these things, most of the hospitals haven't approved any of these things, so we would like to get an idea of how much laboratory modification is required to come into compliance, so that they can close the facilities as early as possible.

MR. SWANSON: I guess I still have a concern about whether you call it qualifying or validating all of your test procedures. Here is the scenario I see. Take something like FDG. We now maybe have 100 different manufacturers, 100 different PET facilities, to get each of the 100 PET facilities validating or qualifying what may be essentially the same test procedures, I mean to me that--I mean it is not like traditional manufacturing where you have one drug product made by one manufacturer.

Can't we think outside of the box here and try to come up with a way to say okay, if you are doing this test procedure this way, under these conditions, there is not a requirement for you to independently, at each site, validate

or qualify the test procedure at least for our traditional products, because this scares me a lot.

DR. KASLIWAL: I think some of the methods, literature has some very good validation. You can probably use that as a reference point.

MR. SWANSON: Who? What?

DR. KASLIWAL: For some of the methods, the literature may have very good validation data. You could use that.

MR. SWANSON: But you are still requiring each of the 100 facilities to do essentially the same thing.

DR. KASLIWAL: You can obtain that centrally if you want at some point, it can be validated centrally and given to you for those conditions, the specific conditions that you use.

DR. BARRIO: That means that a procedure that has been validated by USP, centrally, as you say, will not need localization.

DR. KASLIWAL: For example, the USP method to me seems like it is valid for a no carrier added method of synthesis using acid hydrolysis. FDG, right, that is what it is in the literature and that is where it is coming from.

Now, if you use a very end of that method, under the conditions that you use, for example, in TLC, if you go to basic hydrolysis, whether you can pick up mannose

triflate, which you can form by isomerization under basic conditions, there are literature references for that, but whether your method can pick that up or not, that will be an issue, and at that point we are going to have to see under your conditions of use whether your method is good or not.

DR. BARRIO: We discussed this issue, as you remember, in the context of the USP. If you have a fluoro-mannose, that would be only if you have an electrophilic procedure going on, and the procedures we put in the USP monograph are not the same to detect that isomer.

One aspect of our discussion was if any center decided to use the electrophilic procedure, then, they should provide the procedure to verify the presence of whatever isomer or impurity may exist on that particular procedure.

DR. KASLIWAL: Right, and basically, that is the philosophy we follow, under the method that you use to manufacture and the conditions that you use in the procedure, whether those things are still valid.

MS. AXELRAD: I think that ends our discussion of this draft of the GMPs. I am going to suggest we take a five-minute break, very short, come right back, and spend a little time on the procedures.

[Recess.]

**Approval Procedures Update**

MS. AXELRAD: For this next part of the agenda we are going to try and cover some issues essentially with the approval procedures. We are just going to sort of update you on chemistry, clinical pharmacology, and biopharmaceutics, pediatrics, and user fees, and answer any questions you may have.

Keep in mind that, as I said this morning, what we are doing is developing a guidance document--I don't know if it will be one or two--but basically, that will lay out the procedures for submitting an application under 505(b)(2), which is something that is based on the literature, and also an application under 505(j), and the differences between those are that for (j), you have to demonstrate sameness to a reference listed drug.

So, the first application for ammonia, the first application for O 15 water, the first application that comes in based on a literature review will be a 505(b)(2) application, and after that the next applications that come in, if they can demonstrate sameness to the reference listed drug, the first one that has been approved, or in the case of FDG, sameness to FDG in the Peoria application, then, they could come in as abbreviated new drug applications under 505(j).

Anyway, we are going to lay this all out. There is not a huge amount of difference procedurally between

those two types of applications. They will both have basically the same chemistry submission and they will basically follow that form. We will go through all the different provisions of the regulations - you will have a debarment certification.

We went through these at the February meeting, but the guidance will lay out specifically exactly what you have to do - the patent certifications, the debarment certifications, the financial qualifications of investigators, lots of very, sort of relatively small procedural things in our regulations, and the guidance will sort of step through that for each section of the application.

One of the biggest parts, of course, is the chemistry section, and Ravi is going to tell you what he has been doing in terms of the model chemistry application.

**Chemistry**

DR. KASLIWAL: I think everybody has a copy of the three applications that we would like to have your comments on - the F 18 FDG, N 13 ammonia and F 18 sodium chloride.

F 18 FDG, we discussed that in our last meeting. Since then, we received a number of comments for two ICP, as well as two other people, and we have taken those into consideration and incorporated the relevant comments into this draft.

Basically, each application covers what your drug product is, your components, and what the drug product's quantitative composition is, provides for control of components and raw materials that you use, for reference standards that you may use.

For example, in FDG, if you use a process that is different than some of the compounds that are listed in the reference standard, you don't have to use those. Provides for manufacturing testing facilities. You have to tell us where it is manufactured and where it is tested.

If there is more than one facility within your application, you can include that. Provides of the manufacture of drug substance, what happens in your CPCU, the batch formula that you use, all the controls, and then once the product comes out, how is it formulated, in what vehicle, or whether it is not formulated, it remains as it is you could describe here.

Also, the container/closure information. Accordingly, if you use a pre-sterilized container/closure from a manufacturer in good standing, you could provide accordingly limited information versus if you want to make your own container by container/closure separately, you want a seal and you sterilize it accordingly, the information will need to be much more in nature.

Also, provide for control of finished dosage form

and the description of analytical test procedures, and each procedure, what you need to have. Also, the microbiological validation and the validation data, that needs to be included here.

Basically, in the last discussion what Jane mentioned, a two-page document that is a draft document that is also available on the table, provides a little help, a guidance, what should be included in that section.

There is a table at the end of the batch data, and as I said previously, it provides for the conditions you should store under, your vial. Really, your conditions depend on what you want to label, and how is the product that is going to be shipped then stored, and to support an expiration dating period.

Basically, one batch, if the batch is going to be manufactured within the strength limits of the reference listed drug. That is applicable to the NDA, but if it is a 505(b)(2) application, and you are bringing it especially in the higher strengths than what is listed, then, you are going to have to provide three batch data at the highest rate of concentration.

The current reference listed drug for FDG has a range of 4 to 40 millicuries per mL at the end of synthesis time, so if it is higher than 40 millicuries, you are going to have to bring it up to three batches per mL.

MR. SWANSON: Say that again.

DR. KASLIWAL: The current range of strength is 4 to 40 millicuries per mL at the end of synthesis time.

MR. SWANSON: That is the current NDA?

DR. KASLIWAL: That is the reference listed drug, yes. That's in the package.

MR. SWANSON: How are PET centers going to be made aware of what the characteristics of the current NDA-approved drug are?

DR. KASLIWAL: I think whatever is available in the package insert, that is disclosable, and we can disclose that from the agency's point of view.

MS. AXELRAD: I think that people here in this room are affiliated or associated with this application. One question would be whether the parameters in there, that it eligible as a reference listed drug could be made publicly available, so that people could reference it, and we could give a list of what kinds of information people would need to know.

It is a very different situation than the standard generic, where they way they figure it out, is they go buy the stuff off the shelf and they analyze it. That is the way a generic usually demonstrates that it is the same as the reference listed drug, but this, it is a little difficult to do. So, we ought to find some other way for

the parameters of that reference listed drug to be made known, so people can see whether they are the same or not.

MS. KEPPLER: Is it in the chemistry DMF, and if so, I mean ICP owns it, so we might be able to make it available through the ICP, the characteristics of it. Is everything in the DMF?

MR. KUHS: The original DMF--the NDA has been supplemented once since then--the original DMF contains information at a lower batch strength in a reference to specific concentration at end of bombardment rather than end of synthesis, and the supplement that we filed was specifically to change the range of concentration and the reference to end of synthesis rather than end of bombardment.

MS. KEPPLER: Maybe the two of us could get together and put together a--

MR. KUHS: I don't see a problem with that.

MS. KEPPLER: --a descriptor of the reference listed drug.

DR. KASLIWAL: The criteria for generic, maybe somebody can explain--

MS. AXELRAD: We are going to provide this. We are also probably going to be presenting at the ICP meeting in Vancouver some more details about how you demonstrate sameness, but we can definitely get you a list of the

parameters that need to be known to somebody in order to demonstrate that they are the same, strength, and some of the other characteristics.

If we made those available, then, perhaps you all would be willing to make available to people what they are.

DR. KASLIWAL: But I think whatever that is needed to show that, it is available on the package insert. The other impurities, if present, they can be controlled in guidance document what the limits are allowed.

Basically, after that, a draft copy of the vial and outer packaging labels, and basically a claim for categorical exclusion from performance on EA, and we have provided the statement here, which you can simply fill out.

With FDG, I think the thing that I want to mention is that the model application allows no carrier added method of synthesis, and the specifications are drafted from a point of view that it involves acid hydrolysis, and it is clearly stated if you use any other alternate method of synthesis, then, your specifications and method need to be appropriately evaluated in light of that to show that it's okay.

MS. AXELRAD: Is there any way for us to find out how many people are using the electrophilic process, if anyone? We are hearing nobody, then, I have heard four. Maybe we could ask the question at the ICP meeting.

DR. CALLAHAN: Using electrophilic or a base hydrolysis? Is that two different things? Of course, it is. So, I think we have got a problem here.

MR. JACKSON: Mark Jackson. The only electrophilic that I am still aware of is at Vancouver. They still make FDG in that method. I know of no one in the U.S.

DR. KASLIWAL: They are in Canada, so we don't have to worry about it.

DR. CALLAHAN: Hearing from people that I have discussed it, the base hydrolysis issue is going to become more of an issue.

DR. KASLIWAL: No, the only issue that are published, under basic conditions, depending how you employ, you can have inversion of configuration, and then you are going to have to show that. You could still use it, I am not saying you can't use it, but if you use it, then, you have to show that actually you don't do that.

DR. CONTI: We actually went through these documents in detail, so I might suggest in order to move things along, we actually just go right to some of the points that we had, if that would be reasonable.

DR. KASLIWAL: Fine.

DR. CONTI: Jorge, do you want to lead that, do you want to go through that?

DR. BARRIO: We had a few comments. We were wondering--I was not following this carefully--where the 2 percent fluoride ion impurity came from. Do you remember, Ravi?

DR. KASLIWAL: No. We haven't discussed that in the past, and that is one of the points that I want to discuss. Where it came from was the recommended dose of FDG for scans is 5 to 10 millicurie in the package insert, so if you have 10 millicuries without the limit, and the radiochemical impurity allowed is 90 percent, that means without a limit to that, you can have up to, let's say, a millicurie of free fluoride, you can still pass the product.

At the same time, if you go and look at the package insert of sodium fluoride, the recommended dose for imaging with sodium fluoride is half a millicurie to 2 millicuries. So, we have to the free fluoride amount below what you could get a useful image.

DR. CALLAHAN: I would like to comment on that. That package insert is based to 1974 or something when people were using rectilinear scanners to do bone scans in a planar mode. It has nothing to do with doing PET scans with F 18 fluoride. So, that had more to do with the instrumentation and how much you could get, and it was distributed around the nation, and there were a lot of issues of why that was for I think it was 4 millicuries, as

I recall, because actually, I have been around long enough to actually have dispensed a lot of that material, and that has nothing to do with this and is irrelevant.

If you were doing bone scans with F 18 fluoride, I will defer to--

DR. CONTI: I would say at least 10 millicuries to do a good scan, to do a fluoride bone scan. You can get away with a little less, but--

DR. CALLAHAN: One is an impurity and one is a desired product, so I don't see how they relate. I mean if it is a radiation dosimetry issue or what.

DR. HOUN: Would it interfere in terms of 10 percent sodium fluoride with an FDG product the way it would appear on the scan?

DR. CALLAHAN: Probably not although I can't validate that

DR. CONTI: It can be visualized. The question is does it interfere with the diagnostic quality of the scan, and that is subject to question. I don't know if that is true or not, because you are visualizing bone, which normally you are not going to visualize with an FDG scan for the most part. So, it could potentially interfere.

DR. CALLAHAN: But when the radiochemical purity limit was set in the USP for FDG, I assume that there could be up to 10 percent of something else, and that could be

fluoride or it could be partially hydrolyzed FDG.

So, now, under this guideline, under this application, you could have a 97 percent radiochemical purity and fail, because that would mean you had 3 percent fluoride.

DR. KASLIWAL: Well, the fluoride amount is basically--I explained where it's coming from--the recommended doses, but you are right, you can have a partially hydrolyzed product, as well.

DR. CALLAHAN: I would also challenge that logic to get to that point using the original package insert from sodium fluoride from the mid-seventies.

DR. KASLIWAL: I think that problem that we have is that's the only document, the evidence we have or information we have.

DR. HOUN: We can ask this committee in terms of if sodium fluoride would interfere with the FDG imaging and if that was a possibility, at what limit would people comfortable, or the other issue is that we have to think of the pediatric group, too, and if they were being imaged with FDG and had sodium fluoride, is there a particular concern about their exposure to sodium fluoride you would want to limit.

DR. CALLAHAN: It becomes a radiation dose issue then and the dosimetry from fluoride is different, but still

the critical organ is still the bladder, so if the total administered dose is 10 millicuries of the substance, I bet if you did the numbers, the bladder dose isn't going to be all that different from the contribution from 10 percent fluoride compared to the dose to the bladder already from 10 millicuries of FDG is probably going to be a small factor.

DR. CONTI: The bottom line is no one knows clinically because this has never been studied before to my knowledge. I know people do occasionally combine the tracers because you get anatomical delineation of bone, which is sometimes helpful in the diagnostic test with FDG when you combine the two.

So, that is sort of a trick of the trade, so to speak, but the fact is that there is no clinical data to show at what threshold free fluoride interferes with diagnostic interpretation of an FDG scan that I am aware of.

DR. CALLAHAN: And you do have another document, you have the USP specifications for FDG, which says it allows 10 percent radiochemical impurities.

DR. BARRIO: Sorry for asking the question.

DR. KASLIWAL: Do people see a lot of fluoride in their product?

DR. CALLAHAN: A couple of percent, yes, absolutely.

DR. KASLIWAL: What is the normal level people see

generally?

DR. CALLAHAN: Anywhere from zero to 2 to 2 1/2 percent.

MR. BRESLOW: Good point. We do see counts of zero, which could be fluoride, may not be fluoride, but most likely it is, and it is not unusual to see zero counts and it is not unusual to see 2 percent, 2 1/5 percent on occasion, rare, but it does happen.

MR. KISELEV: May I make another comment? Maxim Kiselev, Eastern Isotopes, Sterling, Virginia.

I think I have a unique experience in this area because we are manufacturing at somewhat higher levels than most other facilities. As far as the release testing is concerned, there is no problem. You can have 99, 98 percent. However, in our experience, the stability of the product is not good enough to maintain over 99 percent over the long period of time.

We have done some extensive stability testing. It appears that the reasonable level which could be achieved without considerable amounts of stabilizer is probably about 95 percent, but if you specify anything more than that, then, they end up either adding stabilizers, which not everybody likes because they are not in use traditionally, and therefore the clinical data may be not relevant to compare with old results, or again having to dilute the